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EXAMINER	
JOHANNSEN, DIANA B	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,647	STEMMER, WILLEM P.C.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10/29/01* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because it includes a claim for benefit under 35 U.S.C. 120 to both a non-provisional application and 3 provisional applications. In the new oath or declaration, the claim for benefit of the 3 provisional applications should be made under 35 U.S.C. 119(e).

It is noted that Applicant's specification includes a claim for benefit of non-provisional application 09/373,333 under 35 U.S.C. 120, and a claim for benefit of provisional applications 60/112,746, 60/111,146, and 60/096,288 under 35 U.S.C. 119(e).

Information Disclosure Statement

2. The information disclosure statement filed October 29, 2001 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Specifically, it is noted that Applicant has not provided -- either in the instant application or in parent application 09/373,333 -- copies of several of the foreign patents cited on the form 1449 filed October 29, 2001 (see the signed and initialed copy of the 1449 provided herewith). Those foreign patents of which copies were not provided by Applicant have not been considered by the

examiner. It is also noted that because only an English abstract of WO 98/42852 has been provided, the notation "abstract only" has been added to the 1449 by the examiner.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, e.g., pages 11, 26). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

4. The title of the invention is not descriptive of the subject matter being claimed in the instant application. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Kits for DNA shuffling.

Claim Objections

5. Claim 10 is objected to because of the following informalities. The claim recites "a DNA polymerase selected from the group consisting of Taq and Klenow." However, the terms "Taq" and "Klenow" alone do not refer to polymerases. This objection could be overcome by amending the claim to recite "....the group consisting of Taq polymerase and Klenow polymerase." Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 15 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is indefinite over the recitation of the limitation "wherein the overlapping fragments are generated by random fragmentation of the pool of related polynucleotide sequences." As the instant claim is drawn to a kit, rather than a method reciting particular steps, it is unclear as to how the recitation of a further limitation on the manner in which fragments are to be produced is intended to further limit the structural and/or functional properties of the claimed product. The claim should be amended so as to make clear the manner in which claim 15 further limits the product of claim 2. For example, this rejection could be overcome by further limiting the "enzyme for converting" of claim 2, (a), to particular enzymes that effect random fragmentation of polynucleotides.

Claim 23 is indefinite over the recitation of the limitation "wherein the kit provides for expression of the shuffled or mutant polynucleotide." First, there is insufficient antecedent basis in the claims for the recitation "the shuffled or mutant polynucleotide." Second, it is unclear as to how the recitation "wherein the kit provides for expression of the shuffled or mutant polynucleotide" is intended to limit the claim. The specification does not define or refer to particular reagents that are considered to "provide for expression" of shuffled/mutant polynucleotides, and the presence of the "enzyme" recited in claim 2 "provides for" production of and subsequent expression of shuffled/mutant polynucleotides. Accordingly, it is unclear as to how or whether the

recitation of claim 23 actual limits the structural and/or functional properties of the claimed product. Clarification is required.

8. It is noted that while the specification does not define the limitation "means for converting a pool of related polynucleotide sequences into overlapping fragments" (see claim 1), the specification describes a variety of reagents and both enzymatic and mechanical methods that may be used in converting pools of related polynucleotides into "overlapping fragments." Accordingly, the specification clearly apprises one of skill in the art as to the scope and meaning of the recitation "means for converting a pool of related polynucleotide sequences into overlapping fragments." Regarding claims 11-12, the specification similarly does not define the limitations "means for purifying the overlapping fragments" in claim 11 and "means for achieving size-based fractionation of the overlapping fragments" in claim 12. However, the specification recites examples of methods that may be employed in "purifying" overlapping fragments (specifically, gel electrophoresis and size exclusion chromatography; see page 40), which methods also achieve size-based fractionation of nucleic acid fragments. As the specification does not otherwise refer to, describe or define methods of or reagents for "purifying" overlapping fragments or size-based fractionation, the disclosure makes clear to those of skill in the art that claims 11-12 are drawn to means for accomplishing gel electrophoresis, size exclusion chromatography, and/or methods known in the art that achieve equivalent separation/purification of nucleic acid fragments and size-based fractionation of fragments, respectively.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-3, 5-6, 8, 15-17, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Milburn et al (U.S. Patent No. 5,256,555 A [10/1993]).

It is first noted that the instant claims are not drawn to a method requiring the performance of particular method steps, but rather to a kit comprising components having particular structural and functional properties. The recitation of the intended use "for DNA shuffling" in claims 1 and 2 does not result in a structural difference between the claimed invention and the kits taught by Milburn et al, and the kits of Milburn et al are capable of performing the intended use recited in the instant claims. (See *MPEP* 2111.02 for a further discussion of the weight given to preamble statements reciting purpose or intended use of a claimed product).

Milburn et al disclose a kit comprising DNase I, an instruction manual, RNA polymerase, and a linearized expression vector (see entire reference, particular column 19, line 22-column 20, line 55, and column 24, lines 7-20). It is an inherent property of DNase I that it constitutes both a "means for" and an "enzyme for" converting "a pool of related polynucleotide sequences into overlapping fragments," as recited in independent claims 1 and 2. (It is noted that the specification at page 42 specifically teaches that conversion of related polynucleotides into overlapping fragments may be accomplished

by DNase I digestion.) Regarding the recitation of instructions "for performing DNA shuffling" in the claims, it is again noted that claims directed to products such as kits are limited by the structural and functional characteristics of the products. The recitation "for performing DNA shuffling" does not alter the properties of the paper or other media on which instructions are contained, and therefore does not differentiate the instructions of the claims from those taught by Milburn et al. Regarding claims 3 and 5, it is an inherent property of DNase I that it is an endonuclease. Regarding claim 15, as discussed above, the recitation "wherein the overlapping fragments are generated by random fragmentation of the pool of related polynucleotide sequences" does not clearly limit the structural or functional properties of the claimed kits. DNase I digestion is not site specific and produces "random fragmentation" of polynucleotides; accordingly, DNase I meets the requirements of claim 15 as written. With respect to claims 16-17, the kit of Milburn et al includes a linearized plasmid containing a *Xenopus* gene under control of a promoter (see, e.g., column 20, lines 45-59). It is an inherent property of this construct that it may be employed to express a gene, which gene may be employed as a marker of transcription/expression; accordingly, the plasmid of Milburn et al meets the requirements of claims 16-17. With respect to claim 23, the kit of Milburn et al includes RNA polymerase, and thereby "provides for expression" of a shuffled or mutant polynucleotide. It is noted that the claim is not limited to particular reagents and that the recitation "provides for expression of the shuffled or mutant polynucleotide" is not, e.g., defined in the specification in such a way so as to limit the claim to particular reagents

or to, e.g., production of mRNA, production of protein, etc. Accordingly, Milburn et al anticipate claims 1-3, 5-6, 8, 15-17, and 23.

11. Claims 1-3, 5, 7-9, 11-19, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by the GibcoBRL Life Technologies™ 1993-1994 Catalogue and Reference Guide (Life Technologies, Inc., 1993, pages 11-2, 11-3, 7-12 and 7-14; hereinafter referred to as "GibcoBRL").

It is noted that the instant claims are not drawn to a method requiring the performance of particular method steps, but rather to a kit comprising components having particular structural and functional properties. The recitation of the intended use "for DNA shuffling" in claims 1 and 2 does not result in a structural difference between the claimed invention and the kits taught by GibcoBRL, and the kits of GibcoBRL are capable of performing the intended use recited in the instant claims. (See *MPEP* 2111.02 for a further discussion of the weight given to preamble statements reciting purpose or intended use of a claimed product).

GibcoBRL teaches a Superscript™ kit comprising primers, dNTP mix, two types of DNA ligase, two types of DNA polymerase, RNase H, nucleic acid size fractionation columns, an instruction manual, and (optionally) a λ expression vector (see entire reference). It is noted that the specification discloses that PCR may be employed in converting related polynucleotides into "overlapping fragments" (see, e.g., page 40). Accordingly, the polymerases, dNTPs and primers taught by GibcoBRL – all reagents that may be employed in PCR – constitute "means for" converting "a pool of related polynucleotide sequences into overlapping fragments," as required by independent

claim 1. Further, each polymerase taught by GibcoBRL constitutes an "enzyme for" converting "a pool of related polynucleotide sequences into overlapping fragments," as required by independent claim 2. Regarding the recitation of instructions "for performing DNA shuffling" in the claims, it is again noted that claims directed to products such as kits are limited by the structural and functional characteristics of the products. The recitation "for performing DNA shuffling" does not alter the properties of the paper or other media on which instructions are contained, and therefore does not differentiate the instructions of the claims from the instruction manual taught by GibcoBRL.

As RNase H is an endonuclease, GibcoBRL's teaching of RNase H meets the requirements of claims 3, 5, and 7. Regarding claims 8-9, GibcoBRL teaches both T4 DNA polymerase and DNA polymerase I. Regarding claims 11-12, the size fractionation columns taught by GibcoBRL constitute both a "means for purifying" overlapping fragments and a "means for achieving size-based fractionation" of overlapping fragments. Specifically, it is noted that it is an inherent property of the size fractionation columns of GibcoBRL that they may be used both to purify nucleic acids from other molecules and reagents, and to separate large nucleic acid fragments from small ones. Regarding claim 13, it is an inherent property of the polymerase, dNTPs and primers taught by GibcoBRL that they are "reagents for PCR amplification." With regard to claim 14, it is an inherent property of any pair of the random hexamers of GibcoBRL, or of any random hexamer in combination with the oligo(dT) primer of GibcoBRL, that these combinations constitute a "pair of PCR primers" that may be employed in PCR amplification. Regarding claim 15, as discussed above, the recitation

"wherein the overlapping fragments are generated by random fragmentation of the pool of related polynucleotide sequences" does not clearly limit the structural or functional properties of the claimed kits. Polymerases, dNTPs and random hexamers may be employed in the production of overlapping random fragments from a pool of related polynucleotides; accordingly, GibcoBRL anticipates the claim as written. Regarding claims 16-18, the kit of GibcoBRL includes an expression vector containing a marker gene (e.g., λgt11 includes the marker gene *B-galactosidase*; see page 7-12). With further respect to claim 18, it is noted that the claim is not limited to, e.g., a pair of primers that specifically amplifies a particular gene; rather the claim is sufficiently broad so as to encompass any "pair of primers for amplifying" any "polynucleotide sequence residing in the expression vector" under any type of conditions. Accordingly, as it is an inherent property of any pair of the random hexamers taught by GibcoBRL that they may be employed in the successful amplification of polynucleotide sequences in any vector, including those of GibcoBRL, under conditions of sufficiently low stringency, the primers of GibcoBRL are sufficient to meet the requirements of the claim as written. With respect to claim 19, the kit of GibcoBRL includes DNA ligases. Regarding claim 23, the kit of GibcoBRL includes an expression vector, and thereby "provides for expression" of a shuffled or mutant polynucleotide. It is noted that the claim is not limited to particular reagents and that the recitation "provides for expression of the shuffled or mutant polynucleotide" is not, e.g., defined in the specification in such a way so as to limit the claim to particular reagents or to, e.g., production of mRNA, production of protein, etc. Accordingly, GibcoBRL anticipates claims 1-3, 5, 7-9, 11-19, and 23.

12. Claims 1-2, 8-9, 13, 15-17, 19, and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by the BioRad "Muta-Gene® Phagemid In Vitro Mutagenesis Version 2 Instruction Manual" (BioRad, January 1997; hereinafter referred to as "BioRad").

It is noted that the instant claims are not drawn to a method requiring the performance of particular method steps, but rather to a kit comprising components having particular structural and functional properties. The recitation of the intended use "for DNA shuffling" in claims 1 and 2 does not result in a structural difference between the claimed invention and the kits taught by BioRad, and the kits of BioRad are capable of performing the intended use recited in the instant claims. (See *MPEP* 2111.02 for a further discussion of the weight given to preamble statements reciting purpose or intended use of a claimed product). It is further noted that the specification discloses that mutagenesis accomplished by annealing and extension of primers using a "Kunkel-type template, consisting of a uracil-containing circular ssDNA" constitutes a step that may be employed to accomplish DNA shuffling (see pages 41-44 of the specification, particular page 44, lines 14-17).

BioRad teaches a kit comprising DNA polymerase, DNA ligase, an "Amber phagemid," a "U-phagemid," and instructions (see entire reference, particularly page 4). It is noted that the specification discloses that PCR may be employed in converting related polynucleotides into "overlapping fragments" (see, e.g., page 40). Accordingly, the DNA polymerase taught by BioRad constitutes both a "means for" and an "enzyme for" converting "a pool of related polynucleotide sequences into overlapping fragments," as required by independent claims 1-2. Regarding the recitation of instructions "for

performing DNA shuffling" in the claims, it is again noted that claims directed to products such as kits are limited by the structural and functional characteristics of the products. The recitation "for performing DNA shuffling" does not alter the properties of the paper or other media on which instructions are contained, and therefore does not differentiate the instructions of the claims from the instruction manual taught by BioRad.

Regarding claims 8-9 and 13, the DNA polymerase of BioRad meets the requirements of the claims. With further respect to claim 13, it is noted that it is an inherent property of any DNA polymerase that it may be employed in PCR; accordingly, the DNA polymerase of BioRad constitutes a "reagent for PCR amplification." Regarding claim 15, as discussed above, the recitation "wherein the overlapping fragments are generated by random fragmentation of the pool of related polynucleotide sequences" does not clearly limit the structural or functional properties of the claimed kits. Polymerases may be employed in the production of overlapping random fragments from a pool of related polynucleotides; accordingly, BioRad anticipates the claim as written. Regarding claims 16-17, the Amber phagemid and the U-phagemid of BioRad each include a promoter and a disrupted *lacZ'* gene; upon reversion of the *lacZ'* amber mutation, the phagemids express functional *lacZ'* (see pages 8-9). Accordingly, the phagemids taught by BioRad constitute expression vectors and include a "marker gene," as required by the claims. With respect to claim 19, the kit of BioRad includes DNA ligase (see page 4). Regarding claims 21-22, Biorad's U-phagemid includes uracils and is employed as a "control template" (see pages 4 and 9). Regarding claim 23, the kit of BioRad includes expression vectors (as discussed above), and thereby

"provides for expression" of a shuffled or mutant polynucleotide. It is noted that the claim is not limited to particular reagents and that the recitation "provides for expression of the shuffled or mutant polynucleotide" is not, e.g., defined in the specification in such a way so as to limit the claim to particular reagents or to, e.g., production of mRNA, production of protein, etc. Accordingly, BioRad anticipates claims 1-2, 8-9, 13, 15-17, 19, and 21-23.

13. Claims 1-5, 8-10, 13-18, 20 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Bauer et al (WO 97/20950 [6/1997]).

It is noted that the instant claims are not drawn to a method requiring the performance of particular method steps, but rather to a kit comprising components having particular structural and functional properties. The recitation of the intended use "for DNA shuffling" in claims 1 and 2 does not result in a structural difference between the claimed invention and the kits taught by Bauer et al, and the kits of Bauer et al are capable of performing the intended use recited in the instant claims. (See *MPEP* 2111.02 for a further discussion of the weight given to preamble statements reciting purpose or intended use of a claimed product). It is further noted that the specification discloses that steps of site-directed mutagenesis may be employed to accomplish DNA shuffling (see, e.g., page 41 of the specification).

Bauer et al teach a kit comprising a DNA polymerase, a restriction endonuclease, dNTPs, "control primers," "control templates," and instructions (see entire reference, particularly pages 5 and 23-24). It is noted that the specification discloses that both restriction enzymes (see, e.g., page 42) and PCR (see, e.g., page 40) may be

employed in converting related polynucleotides into "overlapping fragments." Accordingly, the restriction enzymes, DNA polymerases, dNTPs, and primers taught by Bauer et al constitute "means for" converting "a pool of related polynucleotide sequences into overlapping fragments," as required by independent claim 1. Further, the restriction enzymes and DNA polymerases taught by Bauer et al constitute "enzymes for" converting "a pool of related polynucleotide sequences into overlapping fragments," as required by independent claim 2. Regarding the recitation of instructions "for performing DNA shuffling" in the claims, it is again noted that claims directed to products such as kits are limited by the structural and functional characteristics of the products. The recitation "for performing DNA shuffling" does not alter the properties of the paper or other media on which instructions are contained, and therefore does not differentiate the instructions of the claims from the instructions taught by Bauer et al.

The "selection enzymes" of Bauer et al include restriction enzymes, and meet the requirements of instant claims 3-5 (see pages 23-24; see also the definition of "selection enzyme" on page 9). Regarding claims 8-10 and 20, the DNA polymerases taught by Bauer et al include the thermophilic *Taq* polymerase (see pages 15-16). Regarding claim 13, it is an inherent property of the polymerase, dNTPs and control primers taught by Bauer et al that they are "reagents for PCR amplification." With regard to claim 14, it is an inherent property of the control primers taught and exemplified by Bauer et al that they are a "pair of PCR primers" employed together in amplification (see, e.g., pages 25-26). Regarding claim 15, as discussed above, the recitation "wherein the overlapping fragments are generated by random fragmentation of the pool of related

polynucleotide sequences" does not clearly limit the structural or functional properties of the claimed kits. The restriction enzymes, polymerases, dNTPs and control primers of Bauer et al may all be employed in the production of overlapping random fragments from a pool of related polynucleotides; accordingly, Bauer et al anticipates the claim as written. Regarding claims 16-18, the "control template" taught by Bauer et al is a plasmid that encodes a mutant *lacZ* gene that is corrected by mutagenesis and which, when corrected, expresses functional *lacZ* in *E. coli* (see page 24). Accordingly, the control template of Bauer et al constitutes an expression vector comprising a marker gene. With further respect to claim 18, Bauer et al disclose that their control primers amplify sequences in their control template/plasmid (see pages 24-26). Regarding claim 23, the kit of Bauer et al includes an expression vector (as discussed above), and thereby "provides for expression" of a shuffled or mutant polynucleotide. It is noted that the claim is not limited to particular reagents and that the recitation "provides for expression of the shuffled or mutant polynucleotide" is not, e.g., defined in the specification in such a way so as to limit the claim to particular reagents or to, e.g., production of mRNA, production of protein, etc. Accordingly, Bauer et al anticipate claims 1-5, 8-10, 13-18, 20 and 23.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 4, 7, 9-14, and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Milburn et al (U.S. Patent No. 5,256,555 A [10/1993]) in view of Ahern (The Scientist 9(15):20 [7/1995]).

It is first noted that the instant claims are not drawn to a method requiring the performance of particular method steps, but rather to a kit comprising components having particular structural and functional properties. The recitation of the intended use "for DNA shuffling" does not result in a structural difference between the claimed invention and the kits suggested by Milburn et al in view of Ahern, and the kits of Milburn et al and Ahern are capable of performing the intended use recited in the instant claims. (See *MPEP* 2111.02 for a further discussion of the weight given to preamble statements reciting purpose or intended use of a claimed product).

Milburn et al disclose a kit comprising DNase I, an instruction manual, RNA polymerase, and a linearized expression vector (see entire reference, particular column 19, line 22-column 20, line 55, and column 24, lines 7-20). It is a property of DNase I that it constitutes an "enzyme for" converting "a pool of related polynucleotide sequences into overlapping fragments," as required by the claims. (It is noted that the specification at page 42 specifically teaches that conversion of related polynucleotides into overlapping fragments may be accomplished by DNase I digestion, RNase digestion, restriction digestion, etc.) Regarding the requirement for instructions "for performing DNA shuffling," it is again noted that claims directed to products such as kits are limited by the structural and functional characteristics of the products. The recitation "for performing DNA shuffling" does not alter the properties of the paper or other media

on which instructions are contained, and therefore does not differentiate the instructions of the claims from those taught by Milburn et al.

In addition to disclosing a particular kit that may be used for "*in vitro* RNA transcription" (see, e.g., column 19, lines 24-25), Milburn et al teach improved methods of RNA transcription, and further teach that their methods and reaction mixtures may be employed in performing both RNA transcription and "various other enzymatic reactions in which a polynucleotide is synthesized" (see entire reference, particularly, e.g., column 1, lines 11-14). Specifically, Milburn et al teach methods using:

restriction enzymes and RNase, as recited in instant claims 4 and 7 (see, e.g., column 9, lines 29-59; column 21, lines 25-34);

Taq or Klenow DNA polymerases, as recited in instant claims 9-10 (see, e.g., column 5, line 43-column 6, line 2, particularly column 6, lines 1-2);

agarose and polyacrylamide gel, each of which constitutes a type of "means for purifying" overlapping polynucleotide fragments as recited in claim 11, as well a "means for achieving size-based fractionation" of overlapping polynucleotide fragments, as recited in claim 12 (see, e.g., column 9, line 68-column 10, line 3; column 26, lines 15-38);

polymerase (as discussed above) and pairs of PCR primers, each of which constitute reagents "for PCR amplification," as recited in claims 13-14 (see, e.g., column 6, lines 1-2, lines 42-59; column 17, lines 50-68);

a pair of primers "for amplifying a polynucleotide sequence" in an expression vector, as recited in claim 18 (see, e.g., column 17, lines 50-56);

DNA and/or RNA ligase, as recited in claim 19 (see, e.g., column 19, lines 5-21); and

a thermophilic nucleic acid polymerase, as recited in claim 20 (see, e.g., column 6, line 1, which recites Taq polymerase).

However, Milburn et al do not teach kits including these additional reagents. Ahern teaches that premade reagents provided in kit form are convenient and save researchers time and money (see p. 3/5-4/5). Ahern further teaches that a kit "that supplies all of the necessary reagents for a particular research application" allows practitioners to avoid "browsing through catalogs and buying individual chemicals from one or several suppliers" (see p. 4/5). In view of the teachings of Ahern, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the kits of Milburn et al so as to have prepared kits that further included any or all of the additional reagents taught by Milburn et al, including any or all of the particular reagents taught by Milburn et al set forth above. An ordinary artisan would have been motivated to have made such a modification in order to have provided the reagents needed to perform any or all of the various improved methods of synthesizing polynucleotides taught by Milburn et al to practitioners in a convenient format for the advantages of efficiency and cost-effectiveness, as suggested by Ahern. Regarding claims 11 and 12, it is noted that the specification discloses at page 40 that gel electrophoresis may be employed in purifying overlapping fragments; further, it is a property of gel electrophoresis that it accomplishes size-based fractionation of fragments.

16. Claims 3-5, 7, and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over the BioRad "Muta-Gene® Phagemid In Vitro Mutagenesis Version 2 Instruction Manual" (BioRad, January 1997; hereinafter referred to as "BioRad") in view of Ahern.

It is noted that the instant claims are not drawn to a method requiring the performance of particular method steps, but rather to a kit comprising components having particular structural and functional properties. The recitation of the intended use "for DNA shuffling" does not result in a structural difference between the claimed invention and the kits suggested by BioRad in view of Ahern, and the kits of BioRad and Ahern are capable of performing the intended use recited in the instant claim. (See *MPEP* 2111.02 for a further discussion of the weight given to preamble statements reciting purpose or intended use of a claimed product). It is further noted that the specification discloses that mutagenesis accomplished by annealing and extension of primers using a "Kunkel-type template, consisting of a uracil-containing circular ssDNA" constitutes a step that may be employed to accomplish DNA shuffling (see pages 41-44 of the specification, particular page 44, lines 14-17).

BioRad teaches a kit comprising DNA polymerase, DNA ligase, an "Amber phagemid," a "U-phagemid," and instructions (see entire reference, particularly page 4). It is noted that the specification discloses that PCR may be employed in converting related polynucleotides into "overlapping fragments" (see, e.g., page 40). Accordingly, the DNA polymerase taught by BioRad constitutes an "enzyme for" converting "a pool of related polynucleotide sequences into overlapping fragments," as required by the

claims. Regarding the recitation of instructions "for performing DNA shuffling" in the claims, it is again noted that claims directed to products such as kits are limited by the structural and functional characteristics of the products. The recitation "for performing DNA shuffling" does not alter the properties of the paper or other media on which instructions are contained, and therefore does not differentiate the instructions of the claims from the instruction manual taught by BioRad.

In addition to disclosing a kit for use in *in vitro* mutagenesis, BioRad teaches methods to accomplish *in vitro* mutagenesis and related control assays and other procedures that employ not only the components included in their kit, but additional reagents (see entire reference). Specifically, BioRad teaches:

cloning the "DNA to be mutated" into the pTZ vector using the restriction sites provided in the multiple cloning site of the vector (see page 13 and Figure 2);

the use of RNase A in the growth of uracil-containing phagemids (see pages 17-18, particularly step 7 on page 18); and

gel analysis of reaction products (see pages 22-25).

As the step of cloning into the multiple cloning site of the pTZ vector requires the use of one or more restriction enzymes, the teachings of BioRad indicate that one or more restriction enzymes will be required to practice their methods. Such enzymes meet the requirements of instant claims 3-5. However, BioRad does not disclose the inclusion of such enzymes in their kits. RNase A meets the requirements of instant claims 3, 5, and 7, and the agarose gel employed in the analysis taught by BioRad constitutes both a "means for purifying" overlapping polynucleotide fragments as recited

in claim 11, and a "means for achieving size-based fractionation" of overlapping polynucleotide fragments, as recited in claim 12. However, BioRad does not disclose the inclusion of either RNase A or reagents for performing gel analysis in their kits.

Ahern teaches that premade reagents provided in kit form are convenient and save researchers time and money (see p. 3/5-4/5). Ahern further teaches that a kit "that supplies all of the necessary reagents for a particular research application" allows practitioners to avoid "browsing through catalogs and buying individual chemicals from one or several suppliers" (see p. 4/5). In view of the teachings of Ahern, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the kits of BioRad so as to have prepared kits that further included any or all of the additional reagents taught or suggested by BioRad, including any or all of the particular reagents set forth above. An ordinary artisan would have been motivated to have made such a modification in order to have provided the reagents needed to perform any or all of the various methods and assays disclosed by BioRad to practitioners in a convenient format for the advantages of efficiency and cost-effectiveness, as suggested by Ahern.

Regarding claims 11 and 12, it is again noted that the specification discloses at page 40 that gel electrophoresis may be employed in purifying overlapping fragments; further, it is a property of gel electrophoresis that it accomplishes size-based fractionation of fragments.

Conclusion

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
March 22, 2003